CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-452

CHEMISTRY REVIEW(S)

NDA 20-452

Paraplatin® (Carboplatin Injection)
150 mg per 15 mL
(10 mg/mL)

Bristol-Myers Squibb Company

William C. Timmer, Ph.D.
Division of Oncologic Drug Products
HFD-150

Chemistry Review Data Sheet

1. NDA 20-452

2. REVIEW #1

3. REVIEW DATE: 06/18/03

4. REVIEWER: William C. Timmer, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
IND 25024	01-OCT-84

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
NDA 20-451 / AC	15-OCT-02
NDA 20-451 / AC	04-APR-03

7. NAME & ADDRESS OF APPLICANT:

Name:	Bristol - Myers Squibb Company
Address:	P.O. Box 4000 Princeton, NJ 08543-4000
Representative:	Noemi C. Guma, Ph.D.
Telephone:	609-818-5759

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name:	Paraplatin
Non-Proprietary Name (USAN):	Carboplatin, USP
Code Name/# (ONDC only):	N/A
Chem. Type:	AC: Major Chemistry Amendment
Submission Priority:	S

9. LEGAL BASIS FOR SUBMISSION: N/A.

10. PHARMACOL. CATEGORY: Antineoplastic

11. DOSAGE FORM: Aqueous solution

12. STRENGTH/POTENCY: Three vials sizes containing 50 mg/vial, 150 mg/vial, or 450 mg/vial, diluted to yield a final concentration [for all vials] of 10 mg/mL.

13. ROUTE OF ADMINISTRATION: IV

14. Rx/OTC DISPENSED: _X__Rx ___OTC

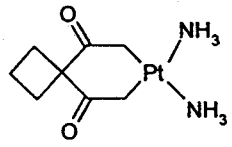
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

cis-Diammine (1,1-cyclobutanedicarboxylato) platinum



Molecular Formula:	$C_6H_{12}N_2O_4Pt$
Molecular Weight:	371.25
CAS Number: CAS No.:	41575-94-4

17. RELATED/SUPPORTING DOCUMENTS:

A. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	25, 024	Carboplatin

B. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	II	[redacted]	[redacted]	3	N/A		
[redacted]	III	[redacted]	[redacted]	4	N/A		
[redacted]	III	[redacted]	[redacted]	4	N/A		

[1] Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

18. STATUS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	08-JUL-03	N/A
Microbiology	Approval	27-MAR-03	D. Hussong, Ph.D.
EA	Categorical Exclusion	09-APR-03	W.C. Timmer, Ph.D.
LNC	N/A	N/A	N/A
Methods Validation	*-- to be initiated --*	09-APR-03	W.C. Timmer, Ph.D.
ODS DMETS	Acceptable	29-MAY-03	D.P. Toyer, Pharm.D.

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for NDA 20-452

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The drug product Paraplatin (Carboplatin Injection) 10 mg/mL is recommended for **APPROVAL.**

- The sponsor has committed to perform a photostability study on the drug product under conditions-of-use. Refer to Addendum, Section IX

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

There are no Phase 4 commitments.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

1. Drug Substance

The drug substance is carboplatin, USP. Since the original NDA filing in March 1994, carboplatin drug substance has become compendial.

Carboplatin is a platinum analog of the cisplatin and shares the same mechanism of action. Their effects have been shown to be cell-cycle non-specific.

Both compounds are alkylating agents and function by forming reactive platinum complexes *in vivo*. These complexes subsequently inhibit DNA synthesis through covalent binding to DNA to form intrastrand, interstrand, and protein crosslinks; however, the primary products are interstrand crosslinks. Aquation of carboplatin, which is thought to produce the active species, occurs at a slower rate than with cisplatin. Nevertheless, both compounds appears to induce an equal number of crosslinks. The difference in potencies between carboplatin and cisplatin appear to be directly related to their differences in aquation rate. These potency differences directly translate into differences in clinical toxicities: cisplatin is nephrotoxic while carboplatin is not.

The drug substance was not reviewed since there were no changes.

2. Drug Product

By way of background, there are three different formulations of Pt-centered antineoplastic compounds that are commercially available and licensed by BMS:

Platinol-AQ Cisplatin NDA 18-057	Paraplatin Solution Carboplatin NDA 20-452
Platinol Cisplatin NDA 18-057	Paraplatin Carboplatin NDA 19-880

The pending approval of Paraplatin solutions will completed the product line for BMS.

This review of this NDA is that of a re-submission to NDA 20-452, Paraplatin® (carboplatin) Injection, 10 mg/mL. NDA 20-452, Paraplatin (carboplatin injection) 10 mg/mL was filed in March 1994 and was subsequently issued a non-approval letter in December 1994. It should be noted that the December 1994 basis for non-approval was solely due to CMC issues.

A regulatory history, detailing the timeline and submissions for these NDAs, is presented in the *Overview* at the beginning of the *Chemistry Assessment*.

Paraplatin solution for injection is a simple admixture of carboplatin and water. The carboplatin solution is then filled into vials, capped and sealed. Except for minor processing aid changes, the basic formulation and manufacturing processes remain unchanged from the original submission. However, in order to bring the submission up to current standards, new potency and impurity assays were developed for analyzing impurities that may be present in the drug product. In addition, a new set of analytical specifications were proposed; updated stability data was also presented in the submission.

B. Description of How the Drug Product is Intended to be Used

Carboplatin is indicated for ovarian cancer.

Ovarian cancer is the sixth most common cancer (other than skin cancer) in women. It ranks fifth as the cause of cancer death in women. The American

Cancer Society estimates that there will be about 25,400 new cases of ovarian cancer in this country in 2003. About 14,300 women will die of the disease; however, the number of new cases of ovarian cancer has been slowly going down since 1991.

The chances of survival from ovarian cancer are better if the cancer is found early. If the cancer is found and treated before it has spread outside the ovary, 95% of women will survive at least five years. However, only 25% of ovarian cancers are found at this early stage. About 78% of all women with ovarian cancer survive at least one year after the cancer is found, and over half survive longer than five years.

There are three types of ovarian cancer; each is named for the type of cells that are involved. Approximately 90 percent of ovarian cancers involve the covering, or epithelium, of the ovaries. This type of cancer is called ovarian epithelial carcinoma. Although some of these tumors are called borderline tumors and usually are not malignant, the majority are invasive and metastasize.[1]

Ovarian tumors grow quickly, but they usually do not cause pain or the symptoms seen with other cancers. Ovarian cancer usually spreads inside the abdominal cavity in the early phase of the illness. Malignant cells may invade the liver, the stomach and/or the diaphragm. In later disease, the cancer can spread through the lymph nodes and blood to other areas of the body, including the lungs and brain. At the time of diagnosis, 33 percent of patients have cancer limited to the ovaries and pelvic area.

Carboplatin is indicated for initial as well as secondary treatment of ovarian cancer due to its superior toxicity profile and equivalent survival benefit compared with other regimens. Results from a recent international trial suggests that carboplatin produces fewer side effects such as hair loss, fever and loss of sensation in the skin. Hence it is preferred over cisplatin as a first-line treatment in ovarian cancer.

C. Basis for Recommendation

From a CMC perspective, BMS has provided sufficient information to support the approval of the drug product. The physical and chemical characteristics, impurity profile, and the stability for carboplatin drug product are adequately demonstrated

[1] The other two less common (~ 5%) types of ovarian cancer are germ cell cancer and stromal tumors. (Germ cells, found in the ovaries, produce the eggs; stroma, the connective tissue found in the ovaries, produces hormones).

in this submission. The acceptance criteria are appropriate ensure the identity, strength, quality, potency and purity of the finished drug product. The criteria are also adequate to assure consistent quality so as to eliminate batch-to-batch variations. In particular, the HPLC assay provides an acceptable separation of carboplatin from its impurities and degradants. Based on analysis of the stability data, the approved shelf-life for Paraplatin solution is 18 months at a storage temperature of 20° - 25°C (69 - 77°F) when protected from light.

III. Administrative

A. Reviewer's Signature

/s/ W. C. Timmer
William C. Timmer, Ph.D.
Review Chemist, HFD-150

Rebecca Wood, Ph.D.
Chemistry Team Leader, HFD-150

File Name: n20452_org.doc

B. Endorsement Block

HFD-150/Chem/WCTimmer
HFD-150/ChemTL/RWood

C. CC Block

Original NDA 20-452

HFD-150/Division File
HFD-150/DD/RPazdur

HFD-810/JSimmons
HFD-810/HPatel

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/s/

William Timmer
7/11/03 02:36:52 PM
CHEMIST

Rebecca Wood
7/11/03 03:11:09 PM
CHEMIST

Dapro dsp

JUN 22 1994

DIVISION OF ONCOLOGY AND PULMONARY DRUG PRODUCTS

REVIEW OF CHEMISTRY, MANUFACTURING AND CONTROLS

NDA #: 20-452
REVIEW # 1

DATE REVIEWED: 5/4/94
REVIEWER: Eva Tolgyesi, Ph.D.

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	3/8/94	3/9/94	3/22/94
AMENDMENT	3/31/94	4/7/94	4/11/94
AMENDMENT	4/7/94	4/8/94	4/11/94

APPLICANT: Bristol-Myers Squibb Company
Pharmaceutical Research Institute
5 Research Parkway, PO Box 5100
Wallingford CT 06492-7660

DRUG PRODUCT'S NAME
Proprietary: Paraplatin — Injection
Established: Carboplatin Injection
Code Name: JM-8, BMY-26575, NSC 241240
Chem.Type/Ther.Class: 3S

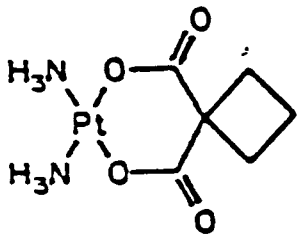
PHARMACOL.CATEGORY/INDICATION: Antineoplastic/ovarian carcinoma

DOSAGE FORM: Sterile aqueous solution in single-dose vials
STRENGTH: 50 mg, 150 mg or 450 mg per vial, 10mg/mL solution

ROUTE OF ADMINISTRATION: IV infusion

Rx/OTC: Rx

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Molecular Formula: $C_6H_{12}N_2O_4Pt$

Molecular Weight: 371.25

Chemical Name: cis-Diammine(1,1-cyclobutanedicarboxylato)platinum

SUPPORTING DOCUMENTS:

DMF — Type II for [redacted] by [redacted]
DMF — Type I for [redacted]
DMF — Type III for [redacted]
DMF — Type III for [redacted]

RELATED DOCUMENTS:

NDA 19-880, Paraplatin for Injection, Bristol-Myers Co.

IND 25,024, Carboplatin for Injection, Bristol-Myers Co.

CONSULTS:

Microbiology Consult Request (HFD-160) filed on 3/24/94
Environmental Assessment Consult Request (HFD-102) filed on 3/24/94
Statistical Consult Request (HFD-715), filed on 3/24/94.

ESTABLISHMENT EVALUATION REQUESTS were filed on 3/23/94.

CONCLUSIONS AND RECOMMENDATIONS:

The application is incomplete and inadequate. Non-approval is recommended. The chemistry deficiencies are listed in Draft Letter to Applicant, Chemist's Part.

ES

Eva Tolgyesi, Ph.D.

5/4/94

cc:
Orig. NDA 20-452
HFD-150/Div. File
HFD-150/ETolgyesi
HFD-150/JBlumenstein
HFD-151/DDaproza
HFD-102/CKumkumian
R/D Init. by:
F/T by:
File: C:\WPFILES\N20452.CR1

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